

Pregnancy-associated listeriosis in England and Wales†

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Received 18 October 2013; Final revision 11 February 2014; Accepted 26 February 2014;
first published online 20 March 2014

SUMMARY

Listeriosis is a rare but severe foodborne disease with low morbidity and high case-fatality rates. Pregnant women, unborn and newborn babies are among the high-risk groups for listeriosis. We examined listeriosis cases reported to the enhanced surveillance system in England and Wales from 1990 to 2010 to identify risk factors influencing outcome. Cases were defined as pregnancy-associated if *Listeria monocytogenes* was isolated from a pregnant woman or newborn infants aged <28 days. Of the 3088 cases reported, pregnancy-associated listeriosis accounted for 462 (15%) cases and 315 cases resulted in a live birth. Several factors were identified as affecting the severity and outcome of listeriosis in pregnancy in both mother and child including: presence or absence of maternal symptoms, gestational age at onset of symptoms, and clinical presentation in the infant (meningitis or septicaemia). Deprivation, ethnicity and molecular serotype had no effect on outcome.

Key words: Epidemiology, gastrointestinal infections, *Listeria*, public health.

INTRODUCTION

Listeriosis is a severe foodborne disease that rarely occurs in humans and primarily affects the elderly, persons with impaired immunity, pregnant women and unborn or newborn babies. Although uncommon, compared to other foodborne infections, listeriosis is associated with high mortality [1]. It is caused by *Listeria monocytogenes*, a Gram-positive bacterium, which is ubiquitous in the environment and also present in many foods. Particular growth characteristics enable the bacterium to survive in food-processing environments and grow in ready-to-eat chilled foods that have an extended shelf life. Currently in the

UK, listeriosis has a higher incidence compared to the 1960s probably due to the increased availability and consumption of such foods [2]. Pregnant women are 18 times more likely to develop the disease following consumption of food contaminated with *L. monocytogenes* as opposed to the general population [3, 4], this is because during pregnancy the immune system is modulated, with the placenta serving as a protective environment for the growth of the bacterium [5]. While pregnant women with listeriosis tend to have mild clinical symptoms or be asymptomatic [6], the infection can have severe outcome for the fetus or newborn infant including miscarriage, still-birth, neonatal sepsis and meningitis [7].

Listeriosis can occur at any time during pregnancy but is most often recognized in the third trimester (from 28 weeks of pregnancy). Pregnancy-related cases of listeriosis are classified into early onset and

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late onset depending on how long after birth the baby starts to develop symptoms. An early onset case is defined as a newborn with symptoms at birth or within 48 h of birth. This is usually attributed to *in-utero* infection either through ascending spread from vaginal colonization, or more commonly through transplacental transmission from maternal bacteraemia. Late onset is defined as a newborn who develops symptoms 48 h after birth. Infection is thought to occur as the baby passes through the birth canal or as a nosocomial infection from another early onset case. Some of the complications of listeriosis in newborns include: physical retardation, granulomatosis infantisepsica or death.

Prior to 1985, an average of 38 cases of listeriosis was reported annually in England and Wales [8]. However, between 1985 and 1989, there was an upsurge in the incidence of listeriosis reaching an average of 200 cases annually, disproportionately affecting pregnant women and neonates, and principally due to the consumption of pâtés from a single manufacturer [9]. As a result of this outbreak, informed health advice can be given to pregnant women [10], building on the advice issued by England's Chief Medical Officer highlighting an increased risk of developing listeriosis after the consumption of pâté and other chilled foods [11].

Following this incident, the number of cases returned to levels seen previously [12]. A further substantial increase in cases occurred between 2001 and 2008, which was primarily seen in older people or those with underlying medical conditions and not in pregnant women [13]. Although the proportion of pregnancy-related cases in England and Wales has remained fairly stable since 1990, there is evidence to suggest an increase in the number of cases in women belonging to ethnic minority groups [14]. The reason for this increase is not clear; however, food consumption habits, socioeconomic status and place of residence may be important factors [15]. This study aims to review all pregnancy-related cases reported over a 21-year period (1990–2010) in order to understand the epidemiology and identify social and clinical risk factors.

METHODS

Case definition

Cases of pregnancy-related listeriosis are defined as pregnant women or newborn infants aged <28 days

from whom *L. monocytogenes* has been isolated from an otherwise sterile site such as the blood, placenta or cerebrospinal fluid. Both mother and child are considered as a single case.

Case ascertainment

Listeriosis case ascertainment is by voluntary electronic reporting of laboratory-confirmed cases to Public Health England Centre for Infectious Disease Surveillance and Control (PHE, CIDSC) and/or by the referral of cultures to Public Health England, Gastrointestinal Bacterial Reference Unit (PHE, GBRU) for identification and subtyping. Clinical and epidemiological data including food history data are requested from the laboratories and local health protection teams, respectively, using standardized questionnaires. Since 2005, additional clinical data have been routinely requested from the consultant medical microbiologist in charge of the case including: principal clinical illness, clinical outcome, antibiotics and other drugs administered. In addition, specific clinical information relating to the pregnancy are required such as: outcome of pregnancy, gestational stage at onset of illness, nature of infant's illness, infant survival, age of infant at onset of illness and evidence of vertical transmission or cross-contamination. The information received is combined and stored in a bespoke Microsoft Access 2007 database and duplicate cases are removed.

Denominator data

Data on the total number of live and stillbirths were obtained from the Office of National Statistics UK and used as denominator data.

Microbiological methods

L. monocytogenes isolates are referred to the UK National Reference Laboratory for *Listeria* (PHE, GBRU) for confirmation of identity and for typing. Prior to 2003, serotyping was performed by agglutination reactions and since then by multiplex PCR as described by Doumith *et al.* [16].

Deprivation

Cases with recorded postcodes of residence were assigned deprivation scores by first assigning them to the correct lower layer super output area (LSOA).

The LSOAs refer to a small geographical area with an average population size of 1500 people (range 1000–3000) for which a deprivation score is calculated using the Index of Multiple Deprivation (IMD) 2007. The IMD 2007 is a composite measure based on 38 indicators grouped in seven domains: income; employment; health deprivation and disability; education, skills and training; barriers to housing and services; crime; living environment. Each domain's contribution to the overall score is weighted differently, with income and employment deprivation weighted the most [17].

Each LSOA in England and Wales is assigned a deprivation score and a rank. The most-deprived areas have *lowest* ranks and *highest* scores. The deprivation scores are then divided into quintiles with 1 being the least deprived and 5 the most deprived.

Statistical analysis

An initial descriptive analysis was performed to describe the cases by outcome of pregnancy according to the following independent variables: ethnicity, *L. monocytogenes* serotype, maternal symptoms, gestational age at onset of symptoms and deprivation. χ^2 for trend was used to quantify the association between these variables and the outcomes of pregnancy (stillbirth/spontaneous abortion, live birth) and for live births, onset of illness (early or late) and survival of the infant.

Where a linear trend was found to exist, a logistic regression model was employed to calculate the odds ratio (OR) and where significant, a multivariate analysis was used to rule out confounding factors. Statistical analyses were conducted using Stata v. 12.1 (StataCorp., USA) and Epi Info v. 3.5.4 (CDC, USA) and a significance level of 0.05 was used as a cut-off point.

RESULTS

Study population

A total of 3088 cases of listeriosis were reported to the PHE enhanced *Listeria* surveillance system during the study period (1990–2010) of which 462 cases (15%) were pregnancy related. The majority of cases were white British (68.6%, 317/462). Serotyping was performed for *L. monocytogenes* isolated from 319 cases of which 70.5% (225/319) were of serotype 4. The presence or absence of maternal symptoms was known for

Table 1. Summary of cases of listeriosis in England and Wales, 1990–2010

Variable	Number (%)
Total number of cases	3088
Pregnancy-related cases	462 (15.0)
Ethnicity	
White British	317 (68.6)
Others	145 (31.4)
Molecular typing	
Serotype 4	225 (70.6)
Serotypes 1/2	92 (28.8)
Maternal symptoms	
Present	176 (68.0)
Absent	83 (32.0)
Deprivation	
1 (least deprived)	47 (15.1)
2	54 (17.4)
3	32 (10.3)
4	82 (26.4)
5 (most deprived)	96 (30.8)
Outcome of pregnancy	
Live birth	315 (68.1)
Stillbirth	35 (7.5)
Miscarriage	66 (14.3)
Still pregnant	5 (1.1)
Unknown	41 (8.9)

259 cases and 67.9% (176/259) reported having symptoms during pregnancy. Of the cases with recorded IMD scores, 30.8% (96/311) lived in the most deprived areas of England and Wales and 15.1% (47/311) lived in the least deprived areas (Table 1). The perinatal mortality rate of listeriosis is known to be high [18] and in this study, it was 100/1000 live births and stillbirths compared to the national average rate of 8.3/1000 of all recorded live births and stillbirths in England and Wales during the same time period.

Outcome of pregnancy

Sixty-eight per cent (315/462) of all pregnancy-related cases resulted in a live birth. A pooled total of 101 cases (21.8%) resulted in either a stillbirth or spontaneous abortion and for five cases (1.1%) pregnancy continued throughout the period of illness. The outcome of pregnancy was unknown for 41 cases (8.9%) (Table 1).

A higher proportion of cases without maternal symptoms resulted in a live birth compared to cases reporting symptoms (symptomatic 72.1%, 119/165; asymptomatic 85.5%, 71/85). The probability of a

live birth was almost halved with the presence of maternal symptoms [$\chi^2=6.71$, OR 0.44, 95% confidence interval (CI) 0.20–0.92, $P=0.01$] compared to cases without maternal symptoms (Table 2).

Gestational age at time of onset was reported for 278 cases. The proportion of live births increased with the gestational age at onset of symptoms in the mother. Six cases reported symptoms in the first trimester and all resulted in either a stillbirth or spontaneous abortion. Eighty-six cases reported symptoms in the second trimester with only 13.9% (12 cases) resulting in a live birth. Of the 186 cases reporting symptoms in the third trimester, 94.6% (176 cases) resulted in a live birth. The odds of a live birth increased by 157 (95% CI 54.9–478, $P<0.0001$) if the mother was infected during the third trimester (Table 2). Even after adjusting for the presence of maternal symptoms, the odds of a live birth still remained high.

Time of illness onset in neonates following live births

Time of illness onset was known for 92% (306/315) of the cases of which 60.7% (186/306) were early onset and 31.1% (120/386) were late onset. Twenty-one per cent (24/113) of cases who reported maternal symptoms resulted in late onset of illness and 35.7% (25/70) of cases without maternal symptoms resulted in late onset. The probability of the infant developing a late onset of illness was twice as high in asymptomatic mothers compared to symptomatic mothers ($\chi^2=4.7$, OR 2.06, 95% CI 1.01–4.23, $P=0.03$) (Table 2).

Gestational age at time of onset did not have any significant association on whether a case had an early or late onset even though 26.3% (45/171) of babies born to mothers that developed symptoms in their third trimester had late onset listeriosis.

Clinical presentation of bacteraemia or *central nervous system* (CNS) involvement was reported for 285 live births. Of the 197 cases of bacteraemia, 19.3% (38/197) had a late onset of illness, while 77.3% (68/88) of the 88 cases presenting with CNS-associated symptoms had a late onset. Cases that presented with late onset listeriosis were 14 times more likely to have CNS symptoms than bacteraemia ($\chi^2=61.1$, OR 14.23, 95% CI 7.41–27.56, $P<0.0001$) (Table 2).

Factors contributing to infant survival

Of the cases with known outcome, 198 survived and 53 died. Eighty per cent (16/20) of the babies infected

during their second trimester died compared to 11.9% (20/167) of babies infected during the third trimester. Babies infected during the third trimester were 22 times more likely to survive compared to babies infected in the second trimester ($\chi^2=53.2$, OR 22.8, 95% CI 5.77–90.02, $P<0.0001$) (Table 2).

Early onset illness increased the odds of survival by 2 compared to late onset illness (OR 2.32, 95% CI 1.05–5.11, $P=0.02$) (Table 2).

Deprivation, ethnicity and *L. monocytogenes* serotype did not have any significant effects on the various outcomes (results not shown).

DISCUSSION

We report a review of pregnancy-related listeriosis over a 21-year period in England and Wales. Pregnancy-related cases make up a small proportion of the total number of reported cases and is similar to the proportion reported in other studies [2, 19].

The severity of impact on the fetus varied with the presence of maternal symptoms. According to our study, mothers who reported having symptoms during pregnancy were more likely to have a stillbirth or spontaneous abortion. This could be because most mothers who reported symptoms were in their first and second trimester or because the *Listeria* dose ingested was high [20]. Spontaneous abortion could also be a result of infection-induced elevated T cells making the body of the mother less hospitable to the fetus [21], although there is evidence to suggest that asymptomatic cases or cases with subclinical symptoms such as non-specific fever result in spontaneous abortion or stillbirth [4]. Animal models have demonstrated that it can take as long as 9 days for the disease in a mother to progress and result in the death of the fetus [22]. The estimated median incubation period for *Listeria* in pregnancy is 27.5 days (range 17–67 days) which is much longer than other clinical forms. A likely explanation is that there is a delay between bacteraemia and infection of the fetus due to the time necessary for *L. monocytogenes* to colonize the placenta and induce fetal infection. This is more likely to occur in human cases where an asymptomatic mother remains undiagnosed. The presence of maternal symptoms was also linked to early onset of disease in the infant, most likely because this was a vertical transmission from mother to child rather than a cross-contamination from another symptomatic baby after birth, as the latter is a rare occurrence.

Table 2. Factors contributing to outcomes of pregnancy, time of illness onset in live births and probability of infant survival

Variables	N (%) Stillbirth and spontaneous abortions (N = 101)	N (%) Live births (N = 315)	Univariate analysis		Multivariate analysis	
			OR of live birth (95% CI)	P value	OR of live birth (95% CI)	P value
Listeriosis symptoms in mother						
Absent	12 (14.5)	71 (85.5)	1.00		1.00	
Present	46 (27.9)	119 (72.1)	0.44 (0.20–0.92)	0.01	0.92 (0.25–3.36)	0.90
Gestational age at time of onset						
First trimester (up to 12 weeks)	6 (100.0)	0				
Second trimester (13–27 weeks)	74 (86.1)	12 (13.9)	1.00		1.00	
Third trimester (28–42 weeks)	7 (3.8)	179 (96.2)	157.69 (54.9–478.0)	<0.0001	179.1 (55.1–581.2)	<0.0001
	Early onset (N = 186)	Late onset (N = 120)				
Maternal symptoms						
Present	89 (78.8)	24 (21.2)	1.00		1.00	
Absent	45 (64.3)	25 (35.7)	2.06 (1.01–4.23)	0.03	0.56 (0.26–1.18)	0.13
Gestational age at time of onset						
Second trimester (13–27 weeks)	11 (91.7)	1 (8.3)	1.00			
Third trimester (28–42 weeks)	128 (74.8)	43 (25.2)	3.70 (0.47–78.76)	0.18		
Presentation						
Bacteraemia only	159 (80.7)	38 (19.3)	1.00		1.00	
CNS presentation	20 (22.7)	68 (77.3)	14.23 (7.41–27.56)	<0.0001	13.8 (1.82–104.4)	0.01
Unknown	7	14				
	Died (N = 53)	Survived (N = 198)				
CNS involvement						
Bacteraemia	37 (21.8)	133 (78.2)	1.00			
CNS	13 (18.6)	57 (81.4)	1.22 (0.57–2.62)	0.57		
Unknown	3	8				
Gestational age at time of onset						
Second trimester (13–27 weeks)	16 (80.0)	4 (20.0)	1.00		1.00	
Third trimester (28–42 weeks)	20 (12.0)	147 (88.0)	22.8 (5.77–90.02)	<0.0001	9.45 (2.07–43.1)	0.004
Onset of illness						
Late onset	17 (22.4)	59 (77.6)	1.00		1.00	
Early onset	17 (11.6)	129 (88.4)	2.32 (1.05–5.11)	0.02	1.66 (0.34–4.85)	0.3

OR, Odds ratio; CI, confidence interval; CNS, central nervous system.

Gestational age at the time of onset is an important predictor for survival of the fetus as the prognosis of the disease is directly proportional to the time of infection during pregnancy. Fetuses affected in early gestation have an increased risk of stillbirth or spontaneous abortion compared to fetuses affected in later gestation [2]. Our results also demonstrate that the 24-week limit of viability is an important predictor for fetal survival with 50% of pregnancies resulting in stillbirth or abortion where the gestational age was <24 weeks [23]. Mothers who reported symptoms in the first or second trimester had spontaneous abortions or stillbirths as a result of the vulnerability of the pregnancy at that stage. Only one pregnancy that ended before the limit of viability (23 weeks) resulted in a live birth; however, the final outcome of the baby is unknown as the case was not followed up after the initial diagnosis.

Furthermore, out of the 33 pregnancies in their second trimester that were over the limit of viability (24–27 weeks), only 11 (33%) resulted in a live birth (results not shown). On the other hand, over 60% of pregnancies in their third trimester and before 37 weeks (age for full-term baby) resulted in a live birth. It is very likely that with or without the presence of *L. monocytogenes*, the chances of a live birth increases as gestational age increases.

For the cases that resulted in live births, we observed that increased gestational age at time of onset of maternal illness and/or birth also influenced the likelihood of infant survival. Infection during the third trimester resulted in a high chance of survival. A likely explanation for this could be that the babies are stronger and their immune system is more developed. Only a small proportion of babies born in their second trimester and after the limit of viability (24–27 weeks) survived. Babies born pre-term, regardless of co-infection, have at least a 50% chance of survival as they are already at risk for several health conditions [2, 24, 25]; therefore, infection with *Listeria* compounds the effects of prematurity.

Time of illness onset in the infant was significantly associated with clinical presentation. Babies who presented with bacteraemia had an early onset of illness which could be explained by the presence of maternal symptoms leading to the early isolation of *L. monocytogenes* from maternal blood [2]. Although we did not look at treatment, it can be argued that the presence of maternal symptoms leads to the early detection of the disease and prompt treatment of the mother or early birth of the baby. This could either

reduce the bacterial load in the baby resulting in a less severe form of fetal invasion which is bacteraemia rather than meningitis or even in the birth of a healthy baby [4]. In a case report [26], a symptomatic pregnant woman delivered a healthy baby following prompt antibiotic treatment even though laboratory results later revealed high numbers of *L. monocytogenes* in the cervical swab. In another study where guinea pigs were used as a proxy for humans [20], *L. monocytogenes* was isolated from fetal liver and brain tissues as early as 2 days after oral inoculation. These reports emphasize the point that early detection and treatment of the mother can improve the outcome of the baby. By contrast, if the baby is born to an asymptomatic mother, infection may occur as the baby passes through the birth canal [24, 27] and this could result in the late onset of illness, and possibly, a CNS presentation. Infection through the birth canal, especially in an untreated mother where vaginal colonization may be high, may lead to a CNS presentation as a result of proximity of the baby's head to the vaginal canal.

Despite the increase seen in pregnant women in ethnic minority groups and the association of listeriosis with neighbourhood deprivation, our results suggest that these factors have no effect on the outcome of listeriosis in either mother or child. This shows that even if ethnicity and deprivation may influence development of the disease, it does not affect the outcome. Possible reasons for this could be that internal factors such as maternal symptoms and clinical presentation are important drivers of the outcome of the disease while external factors such as ethnicity and deprivation play an important part in the initial exposure to the pathogen and predisposition to infection.

We have shown in this study that gestational age at onset and presence of maternal symptoms affects the outcome of the pregnancy while onset of listeriosis (early or late) influences the severity of the impact on the infant. In addition to public health professionals raising awareness of the severity of the disease, antenatal advice given to women should include seeking medical care at the onset of any symptom irrespective of how mild.

As listeriosis increases the chances of premature delivery, it can be classified as a preventable cause of premature birth. Clinicians should consider the possibility of listeriosis as a differential diagnosis in a pregnant woman presenting with fever and actions should be taken towards early treatment with/or without the confirmation of a diagnosis to improve the outcome

of the pregnancy and possibly, the prognosis of the disease in the infant.

Further research is warranted to explore the costs and benefits of routine screening of pregnant women for *L. monocytogenes* with the aim of reducing the burden of disease and improving prognosis through prophylactic treatment.

As the reporting of laboratory cases was voluntary, this may impact our estimations; however, the ascertainment of clinical and exposure data was standardized thereby minimizing the possibility of this form of bias affecting our results. One of the limitations encountered in the study was patients who were still pregnant after diagnosis and treatment were not followed up; hence, the final outcome of the pregnancy was unknown.

ACKNOWLEDGEMENTS

The authors acknowledge the public health professionals, hospital microbiologists and environmental health officers for their contribution to the enhanced surveillance system.

DECLARATION OF INTEREST

None.

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